

Claims

1. A method for treating Alzheimer's disease, comprising,  
contacting a neuronal cell with an amount of a composition comprising one or more  
5 compounds that decrease membrane depolarization of neuronal cells caused by aggregated  
 $\beta$ -amyloid (A $\beta$ ) protein degradation products, effective to decrease the membrane  
depolarization.
- 10 2. The method of claim 1, wherein the membrane depolarization is decreased to about  
80% of its value in the absence of the composition.
- 15 3. The method of claim 1, wherein the membrane depolarization is decreased to about  
75% of its value in the absence of the composition.
- 20 4. The method of claim 1, wherein the membrane depolarization is decreased to about  
70% of its value in the absence of the composition.
- 25 5. The method of claim 1, wherein the membrane depolarization is decreased to about  
65% of its value in the absence of the composition.
6. The method of claim 1, wherein the membrane depolarization is decreased to about  
60% of its value in the absence of the composition.
7. The method of claim 1, wherein the composition comprises one or more compounds  
selected from the group consisting of tyrosine kinase inhibitors, chloride channel antagonists,  
dopamine receptor agonists, and alpha2-adrenergic receptor antagonists.
8. The method of claim 7, wherein the tyrosine kinase inhibitor inhibits EGF receptor  
tyrosine kinase.
- 30 9. The method of claim 8, wherein the tyrosine kinase inhibitor is selected from the  
group consisting of 4,5-dianilinophthalimide (DAPH1) and tyrphostin 47.

10. The method of claim 7, wherein the tyrosine kinase inhibitor inhibits TrkA receptor tyrosine kinase.

5 11. The method of claim 10, wherein the tyrosine kinase inhibitor is tyrphostin AG879.

12. The method of claim 7, wherein the chloride channel antagonist is selected from the group consisting of nafoxidine and clomiphen.

10 13. The method of claim 7, wherein the dopamine receptor agonist is selected from the group consisting of SKF81297, vanillyl-mandelic acid and dopamine.

14. The method of claim 7, wherein the alpha2-adrenergic receptor antagonist is rauwolscine.

15 15. The method of claim 1, wherein the subject is free of symptoms otherwise calling for treatment with the composition.

16. A method for treating a subject having a condition characterized by neuronal  
20 membrane depolarization, comprising  
administering to a subject in need of such treatment a composition selected from the group consisting of tyrosine kinase inhibitors, chloride channel antagonists, dopamine receptor agonists, and alpha2-adrenergic receptor antagonists in an amount effective to reduce membrane depolarization, wherein the subject is free of symptoms otherwise calling for  
25 treatment with the composition.

17. The method of claim 16, wherein the membrane depolarization is decreased to about 80% of its value in the absence of the composition.

30 18. The method of claim 16, wherein the membrane depolarization is decreased to about 75% of its value in the absence of the composition.

19. The method of claim 16, wherein the membrane depolarization is decreased to about 70% of its value in the absence of the composition.
20. The method of claim 16, wherein the membrane depolarization is decreased to about 65% of its value in the absence of the composition.
21. The method of claim 16, wherein the membrane depolarization is decreased to about 60% of its value in the absence of the composition.
22. The method of claim 16, wherein the tyrosine kinase inhibitor inhibits EGF receptor tyrosine kinase.
23. The method of claim 22, wherein the tyrosine kinase inhibitor is selected from the group consisting of 4,5-dianilinophthalimide (DAPH1) and tyrphostin 47.
24. The method of claim 16, wherein the tyrosine kinase inhibitor inhibits TrkA receptor tyrosine kinase.
25. The method of claim 24, wherein the tyrosine kinase inhibitor is tyrphostin AG879.
26. The method of claim 16, wherein the chloride channel antagonist is selected from the group consisting of nafoxidine and clomiphen.
27. The method of claim 16, wherein the dopamine receptor agonist is selected from the group consisting of SKF81297, vanillyl-mandelic acid and dopamine.
28. The method of claim 16, wherein the alpha2-adrenergic receptor antagonist is rauwolscine.
29. A composition comprising  
one or more compounds that decrease membrane depolarization of neuronal cells caused by aggregated  $\beta$ -amyloid ( $A\beta$ ) protein degradation products, and

one or more compounds that decrease calcium influx of neuronal cells caused by aggregated  $\beta$ -amyloid ( $A\beta$ ) protein degradation products.

30. The composition of claim 29 further comprising a secretase inhibitor.

31. A composition comprising  
one or more compounds that decrease membrane depolarization of neuronal cells caused by aggregated  $\beta$ -amyloid ( $A\beta$ ) protein degradation products, and  
a secretase inhibitor.

32. A composition comprising  
one or more compounds that decrease calcium influx in neuronal cells caused by aggregated  $\beta$ -amyloid ( $A\beta$ ) protein degradation products, and  
a secretase inhibitor.

33. A method for treating Alzheimer's disease, comprising  
administering an  $A\beta$  vaccine to a subject in need of such treatment,  
administering to the subject an amount of a neuronal membrane depolarization inhibitor effective to inhibit membrane depolarization.

34. A method for treating Alzheimer's disease, comprising  
administering an  $A\beta$  vaccine to a subject in need of such treatment,  
administering to the subject an effective amount of the composition of claim 29.

35. A method for treating Alzheimer's disease, comprising  
administering an  $A\beta$  vaccine to a subject in need of such treatment,  
administering to the subject an effective amount of the composition of claim 30.

36. A method for treating Alzheimer's disease, comprising  
administering an  $A\beta$  vaccine to a subject in need of such treatment,  
administering to the subject an effective amount of the composition of claim 31.

37. A method for treating Alzheimer's disease, comprising  
administering an A $\beta$  vaccine to a subject in need of such treatment,  
administering to the subject an effective amount of the composition of claim 32.
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38. A method for treating Alzheimer's disease, comprising  
administering to the subject an effective amount of the composition of claim 29.
39. A method for treating Alzheimer's disease, comprising  
administering to the subject an effective amount of the composition of claim 30.
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40. A method for treating Alzheimer's disease, comprising  
administering to the subject an effective amount of the composition of claim 31.
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41. A method for treating Alzheimer's disease, comprising  
administering to the subject an effective amount of the composition of claim 32.
42. A method for identifying lead compounds for a pharmacological agent useful in the  
treatment of conditions associated with increased neuronal depolarization induced by the  
20 presence of  $\beta$ -amyloid peptide (A $\beta$ ) aggregates, comprising  
providing a neuronal cell in a medium containing a potentiometric compound,  
wherein the influx into the neuronal cell of the potentiometric compound upon depolarization  
of the neuronal cell is detectable,  
contacting the neuronal cell with A $\beta$  aggregates under conditions which permit influx  
25 of a control amount of the potentiometric compound into the neuronal cell,  
contacting the neuronal cell with a candidate pharmacological agent, and  
detecting the potentiometric compound in the neuronal cell as a measure of the  
relative depolarization of the neuronal cell in the presence of the candidate pharmacological  
agent, wherein detection of a lesser amount of potentiometric compound in the neuronal cell  
30 than is present when the neuronal cell is contacted with A $\beta$  aggregates but not the candidate  
pharmacological agent indicates that the candidate pharmacological agent is a lead compound  
for a pharmacological agent which reduces A $\beta$  aggregate induced neuronal cell

depolarization.

43. The method of claim 42 wherein the candidate pharmacological agent is a peptide.

5 44. The method of claim 42 wherein the candidate pharmacological agent is a small organic molecule.

45. The method of claim 42, wherein the potentiometric compound is fluorescent.

10 46. The method of claim 45, wherein the potentiometric compound is bis-(1,3-dibutylbarbituric acid)trimethine oxonol (DiBAC<sub>4</sub>(3)).

15 47. The method of claim 42, further comprising a control wherein the neuronal cell is not contacted with the A $\beta$  aggregates.

20 48. The method of claim 42, further comprising a control wherein the neuronal cell is not contacted with the candidate pharmacological agent.